



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/10, 47/24	A1	(11) International Publication Number: WO 00/25822
		(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/US98/23014	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 29 October 1998 (29.10.98)	
(71)(72) Applicants and Inventors: GRASELA, John, C. [US/US]; 4521 Saluto Court, San Diego, CA 92130 (US). GRASELA, Joseph, C. [US/US]; 4767 Ocean Boulevard, San Diego, CA 92109 (US). JUBENVILLE, Robert, M. [US/US]; 550 Washington Street, San Diego, CA 92103 (US). McCLOSKEY, Joseph, J. [US/US]; 1167 Copperwood, Bloomfield Hills, MI 48302 (US).	

(74) Agents: MCCLAIN, James, W. et al.; Brown, Martin, Haller & McClain, 1660 Union Street, San Diego, CA 92101-2926 (US).

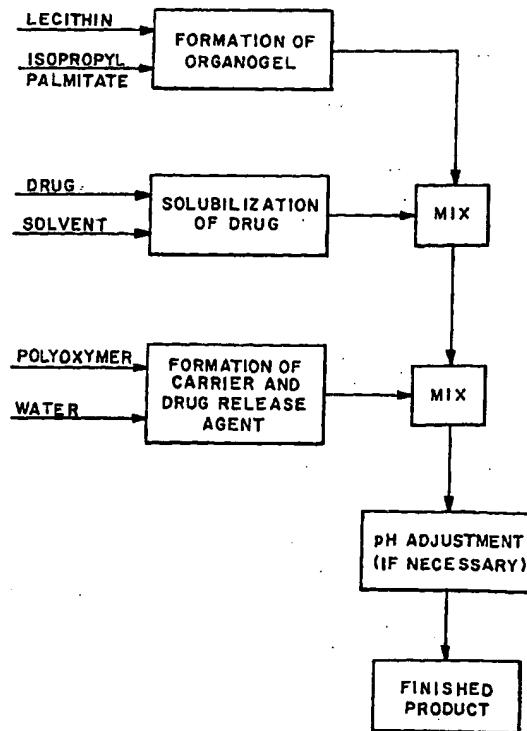
Published

With international search report.

(54) Title: TRANSDERMAL DELIVERY OF MEDICATIONS USING A COMBINATION OF PENETRATION ENHancers

(57) Abstract

A composition and procedures for its formation and administration are described, which provide for a convenient, efficacious and simple transdermal administration of medications from a topically applied cream. No transmission through a membrane is involved. The composition incorporates at least two separate penetration enhancers which function synergistically to provide for rapid but controllable transport of the medication from the cream into the skin. The use of a plurality of penetration enhancers, at least one of which facilitates the separation of medication from the cream and at least a second of which alters the structure of the outer layers of skin, particularly the stratum corneum, enhances migration of the drug through the stratum corneum.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

TRANSDERMAL DELIVERY OF MEDICATIONS USING A COMBINATION OF PENETRATION ENHANCERS

BACKGROUND OF THE INVENTION

5 *Field of the Invention:*

The invention herein relates to the transdermal delivery of medications to a patient. More particularly it relates to compositions which allow medication molecules to be solubilized and delivered transdermally and to methods for formation of such compositions and for their therapeutic use.

10 (For convenience herein the terms "drug" and "medication" may be used interchangeably. We wish to emphasize, however, that this invention is applicable to the delivery of any type of compound or molecular species which is intended to be administered to a patient transdermally for a therapeutic or physiological purpose. Whether the material happens to meet a particular specific definition of a "drug" or "medication" or other applicable term is not critical for the purposes of this invention, and the invention should not be limited by the particular term applied to the material being administered.)

15 *Description of the Prior Art:*

In the past the delivery of medications transdermally to a patient has been limited to administration by transcutaneous injection or by transdermal migration from a patch placed on the outer surface of the patient's skin. The deficiencies of administration by injection are obvious. With only a few exceptions injections must be administered by trained and qualified medical personnel. The injection itself causes a break in the skin which can lead to infection, despite precautions; 20 an injection needle may itself be contaminated causing infection to the patient; and, course, it is a simple fact that injections are uncomfortable to almost all patients. Further, an injection is normally not "location specific." Rather the injection is made at a location on the body remote from the affected area, and 25 the injected medication must be transported through the body to that location.

-2-

This results in losses in transport, so that to administer an effective amount of medication to the affected area, and excess of medication must be injected.

In view of these deficiencies of injection administration, significant effort has been spent in the last few years in seeking alternative methods of 5 transdermal administration of medications. It has been necessary to meet two requirements. First, the method must provide for extended containment of the drug and any carrier while in place on the patient's skin (in effect analogous to containment of the medication and carrier in the reservoir vial of the injection syringe), in a form that does not lend itself either to contamination of the 10 medication and carrier or to loss of the medication and carrier. Second, the systems employed must provide for a regulated and predictable rate of transfer of the medication (with or without the carrier) from the containment device into and through at least some layers of skin to where the medication will be dispersed throughout the affected area of the body.

15 The only workable prior art embodiment of such a device has been what is commonly known as a "patch." A patch is generally a flat hollow device with a permeable membrane on one side and also some form of adhesive to maintain the patch in place on the patient's skin, with the membrane in contact with the skin so that the medication can permeate out of the patch reservoir and into and 20 through the skin. The outer side the patch is formed of an impermeable layer of material, and the membrane side and the outer side are joined around the perimeter of the patch, forming a reservoir for the medication and carrier between the two layers.

Numerous kinds of medications have been administered through the use 25 of a patch, notably scopolamine for preventing motion sickness, nicotine derivatives intended to discourage an addicted smoker from continuing the smoking habit and estrogen hormones.

Patches have their own set of disadvantages. A principal disadvantage is that, notwithstanding the presence of a penetration enhancer, the delivery of

-3-

the medication is necessarily limited by the rate of passage of the medication through the patch membrane to the skin. Since the medication is not in contact with the skin while it is enclosed in the patch, whatever length of time is required for the medication to permeate through the skin itself to become effective is 5 necessarily lengthened by the time needed for the medication first to exit from the patch through the membrane. In many cases the membrane permeation rate is the significant rate limiting step of speed of effectiveness of a particular medication, and can render patch administration essentially ineffective because the medication cannot reach the patient's system rapidly enough to be 10 efficacious. In addition, the adhesive which is intended to secure the patch to the patient's skin can fail, so that the patch disengages from the skin before completion of the transfer of the medication, resulting in loss of that quantity of medication which remains within the patch's reservoir.

Various methods have been used to increase skin permeation of 15 medications, including penetration enhancers, pro drugs, superfluous vehicles, iontophoresis, phonophoresis and thermophoresis. For the purposes of this invention, only the penetration enhancers are relevant. Ideal enhancers have no irritancy and toxicity to the skin, and the whole body, together with having high enhancing effects. Enhancers themselves should be physiochemically 20 stable and not have pharmacologic effects, and preferably should not have smell, color, or taste. A typical example of an enhancer is disclosed in U.S. Patent No. 4,783,450 (to Fawzi et al.) in which lecithin is used for penetration enhancement.

The stratum corneum provides the principal barrier to the percutaneous 25 penetration of topically applied substances. It is the most superficial cutaneous layer and is a horny layer that consists of flat, scalelike "squames" made up of the fibrous protein keratin. The squames are continually being replaced from below by epidermal cells that die in the process of manufacturing keratin. It is unlikely that the emulsified fat on the skin surface greatly affects permeability.

-4-

However, vehicles can control, to a great extent, the rate of penetration of drugs that are applied to the skin. The intercellular lipids may be important for the permeability barrier in skin.

It is known that some combinations of enhancers and vehicles act 5 synergistically, such as the combination of ethanol as a vehicle for the enhancer laurocapram. However, many combinations are not synergistic; for instance, n-decylmethylsulfoxide lowers the zeta potential of the skin, and thus enhancement due to conduction flow (iontophoresis) is minimized. In the past, synergism of combinations could not be predicted.

10 Further, one must differentiate between penetration enhancer which act to improve the ability of the medication to pass through a patch membrane to reach the skin, and those which act to enhance the separation of the medication from its carrier matrix or to enhance the diffusion of the medication into and through the skin.

15 However, notwithstanding the various deficiencies mentioned, administration by injection or by patch remain only by viable transdermal administration techniques known to the prior art.

SUMMARY OF THE INVENTION

20 We have now developed a system that provides for a convenient, efficacious and simple system for transdermal administration of medications in which the medication is present in a composition for direct application to the skin, commonly in the form of a cream or similar material. The transdermal administration of the drug is therefore not hindered by having to penetrate a 25 patch membrane, since the cream and its medication content are directly in contact with the skin and the medication needs only to separate from the cream in order to be available for transdermal migration. In addition, since the composition is in the form of a cream or other viscous moldable and spreadable material, the drug may be effectively administered by application of the cream

to many bodily areas where a patch either will not fit or cannot be shaped to conform to the skin contours.

(As with the use of the terms "medication" and "drug," our invention is not to be limited by the term used to describe the physical properties of the 5 composition herein. We will for convenience use the term "cream," but other terms such as "gel," "lotion," "paste" and the like also could be applicable. As will be seen from the description below, the physical nature of the composition containing the medication and to be applied to the patient's skin will be defined by functional parameters, rather than being limited by an arbitrary descriptive 10 term.)

A key element in the success of the present invention is our discovery that the use of at least two separate penetration enhancers of defined function results in a synergism which provides rapid but controllable separation of the medication from the cream and its penetration into and within or through the skin. At least 15 one of the penetration enhancers acts to facilitate the separation of drug from the carrier within the cream and at least a second penetration enhancer alters the structure of the outer layers of skin, particularly the stratum corneum, such that migration of the drug through the stratum corneum is enhanced and expedited. The medication is thus taken up by the patient's system and is efficacious much 20 more rapidly than would be the case for administration of the medication by means of the prior art patch system. Further, although permeation of the skin does not provide for as rapid administration by the medication as would result from direct injection, the use of the present invention avoids the problems 25 associated with injection administration.

Therefore, in one principal embodiment, the invention is of a composition for diffusional transdermal delivery of medication to a patient, which comprises a medication capable of being administered transdermally; a carrier for the medication; a first penetration enhancer which improves diffusion of the medication into and within the patient's skin; and a second penetration enhancer

-6-

which improves diffusion of the medication out of the composition for transdermal migration; the composition having a viscosity in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered
5 transdermally to the patient.

In another principal embodiment, the invention is of a method for the preparation of a therapeutic composition to be transdermally administered which comprises solubilizing a medication capable of being administered transdermally; forming an organogel comprising a first penetration enhancer which improves
10 diffusion of the medication into and within the patient's skin, and a carrier for the solubilized medication; forming a polymeric component comprising a second penetration enhancer which improves diffusion of the medication out of the composition for transdermal migration; and blending the solubilized medication, organogel and polymeric component to form the composition having a viscosity
15 in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient.

In yet another principal embodiment, the invention is of a method for the transdermal administration of a medication which comprises solubilizing a
20 medication capable of being administered transdermally; forming an organogel comprising a first penetration enhancer which improves diffusion of the medication into and within the patient's skin, and a carrier for the solubilized medication; forming a polymeric component comprising a second penetration enhancer which improves diffusion of the medication out of the composition for
25 transdermal migration; blending the solubilized medication, organogel and polymeric component to form the composition having a viscosity in a range such that it may be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient; and applying the composition to the skin

-7-

of a patient for the period of time and allowing the medication to diffuse out of the composition and through the skin, such that the medication is taken up by the body of the patient and acts therapeutically on the patient.

In preferred embodiments the first penetration enhancer is a lecithin 5 organogel formed with isopropyl palmitate or isopropyl myristate, and the second penetration enhancer is a polyoxymer, preferably a polyoxyalkylene derivative of propylene glycol. A wide variety of medications can be delivered by this invention. Further, while the invention herein is described in terms of the minimum number of synergistically acting penetration enhancers (i.e., two), it will 10 be understood that additional penetration enhancers can also be present. Thus there may be more than one enhancer which operates with a specific mechanism, or there may be additional enhancers which provide yet other modes of operation, or both.

The methods and compositions described herein provide a unique and 15 highly effective technique for administering medication directly to an affected area of the body with the minimum amount of medication and with the avoidance of unwanted side effects. Unlike administration by injection or orally, the transdermal administration herein is site specific; the cream is applied to the skin directly at the affected area of the body. There are therefore no losses of 20 medication during transport from a remote application site. Similarly, the long delays in having an effective quantity of the medication reach the affected area of the body, which are inherent in injection and oral administration, are entirely eliminated in the present invention.

The present method also avoids unwanted side effects. For instance, in 25 oral administration of a medication, the medication itself can adversely affect the gastrointestinal tract as it is swallowed and dissolved for assimilation into the circulatory system. Those skilled in the art are well familiar with the common caution required for many oral medications that they must be administered only in conjunction with a meal, or, conversely, that they cannot be administered in

-8-

the presence of specific types of food products, such as dairy products. These cautions are necessary since the orally administered medication's efficacy will be adversely affected by certain foods, or the person's gastrointestinal tract will be irritated by the medication if the latter is not diluted by the presence of food 5 in the gastrointestinal tract. Such considerations are, of course, entirely absent in the present invention, where the same medications can be easily and conveniently administered transdermally without incurring such side effects.

Further, the transdermal administration avoids the "first pass effect," which often results when a medication is administered orally and thus has to 10 pass through various organs, including the liver, before reaching the affected area of the body. These organs can absorb or chemically alter significant quantities of the passing medication, thus requiring that large excess quantities of the medication be administered initially to insure that an effective quantity of the medication will ultimately reach the affected area of the body. Since in this 15 method the medication commonly passes through the skin directly to the affected site, there is no problem of loss in intermediate organs, and therefore excessive quantities of medication do not need to be delivered to counter such losses. (As an example, ketoprofen is commonly administered orally in quantities of about 50-75 mg per dose for the desired efficacy. In the present 20 invention, however, an equally effective dose of ketoprofen can be delivered by topical transdermal administration of only 3 mg.)

Finally, since the present invention is site specific, the depth of delivery of the medication can be readily controlled, as contrasted to injection delivery.

25

BRIEF SUMMARY OF THE DRAWING

The single Figure of the drawing is a flow chart illustrating schematically formulation of a preferred embodiment of a composition of this invention.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The unique compositions of the present invention require a specific sequence of steps in their formation if a therapeutically effective and pharmaceutically compatible composition is to be obtained. This is best 5 understood by reference to the Figure of the drawing.

The basic composition of this invention is a mixture of an organogel, a solubilized medication or drug and a carrier combined with a drug release agent. Penetration enhancement is provided by the organogel and by the release agent.

10 In the exemplary process as illustrated in the Figure, an organogel is formed, in this example from lecithin and isopropyl palmitate. These two materials are thoroughly blended and mixed until a substantially uniform gel structure forms. The organogel, which is the base for the cream composition, should be formed at the time that the composition is to be formulated. The drug 15 or medication is solubilized with a solvent, such as water, alcohol or other appropriate solvent, again by mixing in a known manner. When it is desired to start formation of the actual composition, the solubilized drug is mixed thoroughly into the organogel matrix, again by conventional mixing techniques. The technique used will of course be such that the organogel's structure is not 20 broken down. Finally, a carrier, such as water or alcohol, and a drug release agent, such as a polyoxymer, are blended. The carrier/release agent mixture can be made up in large lots and stored under refrigerator until needed, at which time an appropriate quantity can be taken for and the remainder retained in refrigerated storage. The carrier/release agent mixture is then mixed with the 25 drug/organogel mixture to produce the final "cream" composition. Details will be provided below.

Considering first the organogel, the blend of the two components will be in the range of from about 25% to 75% of the lecithin component, the remainder being the fatty acid ester component. (Unless stated otherwise, all percentages,

-10-

parts and concentrations are by weight.) The "lecithin component" may be lecithin, any comparable fatty acid phospholipid emulsifying agent, such as fatty acids and their esters, cholesterol, tri-glycerides, gelatin, acacia, soybean oil, rapeseed oil, cottonseed oil, waxes or egg yolk, or any other material which acts

5 in the same manner as lecithin.

The other component is an organic solvent/emollient, particularly including fatty acid esters, of which the esters of the saturated alkyl acids are preferred.

The preferred solvent/emollient in the present invention is isopropyl palmitate or isopropyl myristate. However, there are numerous compounds available which

10 exist in liquid form at ambient temperatures and will function in a manner equivalent to the fatty acid esters. These are all quite well known and described.

They include, but are not limited to, the following:

	Ethanol	Laurocapram (azone)
	Propylene glycol	(1;1-dodecylazacycloheptan-2-one)
15	Water	
	Sodium oleate	Acetonitrile
	Leucinic acid	1-decanol
	Oleic acid	2-pyrrolidone
	Capric acid	N-methylpyrrolidone
20	Sodium caprate	N-ethyl-1-pyrrolidone
	Lauric acid	1-methyl-2-pyrrolidone
	Sodium laurate	1-lauryl-2-pyrrolidone
	Neodecanoic acid	Sucrose monooleate
	Dodecylamine	Dimethylsulfoxide
25	Cetyl lactate	Decylmethylsulfoxide
	Myristyl lactate	Acetone
	Lauryl lactate	Polyethylene glycol (100-400mw)
	Methyl laurate	Dimethylacetamide
	Phenyl ethanol	Dimethylformamide
30	Hexamethylene lauramide	Dimethylisoboride
	Urea and derivatives	Sodium bicarbonate
	Dodecyl n,n-dimethylamino acetate	Various C ₇ to C ₁₆ alkanes
	Hydroxyethyl lactamide	Mentane
	Phyophatidylcholine	Menthone
35	Setsol-318 (a medium chain glyceride)	Menthol
	Isopropyl myristate	Terpinene
	Isopropyl palmitate	D-terpinene
	Surfactants (including):	Dipentene
	polyoxyethylene (10) lauryl ether	N-nonalol
40	diethyleneglycol lauryl ether	Limonene
		Ethoxy diglycol

-11-

This combination of the phospholipid emulsifying agent and the fatty acid or fatty acid ester or equivalent thereof forms an organogel. In the example referred to in the Figure, the organogel will be a lecithin organogel, which is both isotropic and thermally reversible. At temperatures greater than about 40°C the 5 organogel will become a liquid and its viscosity will be greatly reduced. Water can be also be added to control the viscosity of the organogel. The organogel serves as one of the penetration enhancers in the cream, and acts on the stratum corneum of the skin to promote interaction between the phospholipids of the cream and the phospholipids of the skin. This causes a disruption in the 10 normal regular arrangement of layers in lipids in the stratum corneum so that openings are created which then allow the drug to pass more easily through the skin. The organogel will be compatible with a wide variety of lipophilic, hydrophilic and amphoteric drugs and medications.

Using the above-described lecithin organogel and its components as an 15 example, the properties needed for inclusion of a components in this invention will be evident. The various compounds, polymers, etc. comprising the organogel, the solubilized drug and the carrier/polyoxymer components must all be compatible with each other, so that chemical reactions do not occur which would adversely affect the efficacy or safety of the cream composition; they must 20 be mutually soluble so that they can be mixed and blended to a uniform consistency; they must be such that the resulting cream composition has a viscosity under ambient conditions which is low enough to allow it to be applied easily and smoothly to the skin, but not so low that the cream acts as at least in part like a liquid and cannot be retained on the skin where it is applied; they must 25 not be toxic, irritating or otherwise harmful to the patient; they must be sufficiently stable that the overall composition will have a reasonable shelf life and service life; and, as a practical matter, they must be available at reasonable cost. Thus, it will generally be found that the characteristics of a drug or medication which make it difficult to administer transdermally through the present

-12-

system include its having low stability, particularly at ambient temperatures; not being soluble in the composition; having high molecular weight resulting in difficulty penetrating the stratum corneum, even with the enhanced openings; and/or causing an adverse reaction with the one or more skin layers.

5 The drug or medication which is to be administered usually must be solubilized in a solvent to enable it be blended properly with the organogel and the carrier/release agent. Typical solvents for such use include water, the low molecular weight alcohols and other low molecular weight organic solvents. Solvents such as water, methanol, ethanol and the like are preferred. The
10 purpose of solubilizing is to enable the medication to become properly dispersed in the final cream. It is possible that a few drugs or medications might themselves be sufficiently soluble in the cream that a solvent, and therefore a separate solubilizing step, would not be needed. For the purpose of this description, therefore, the term "solubilized" drug or medication shall be
15 considered to include those drugs or medications which can be dispersed or dissolved into the cream with or without the presence of a separate solvent. Usually the amount each of medication and solvent which will be present, based on the entire composition, will be in the range of up to <1%-20%, with the preferred concentration of each being about 10%. The concentrations of both
20 need not be identical.

 A wide variety of drugs may be transported by this method and through this type of composition. Typical of the various drugs which can be successfully incorporated into the present composition and transdermally transported include the following classes of substances:

-13-

	Antidiabetic Agents	Multivitamin Preparations
	Sulfonylureas	Vitamin Combinations
5	Acetohexamide Chlorpropamide Tolazamide Tolbutamide Glipizide Glyburide Glimepiride	Antihyperlipidemic Agents
10	Metformin Acarbose Insulin	Fluvastatin Lovastatin Pravastatin Simvastatin Probuco ^l Niacin Dexothyroxine Clofibrate Gemfibrozil
15	Glucose Elevating Agents	Cardiac Drugs
	Diazoxide Glucose	Cardiac Glycosides
20	Thyroid Hormones	Digitoxin Digoxin
	Levothyroxine Liothyronine Thyroid USP Thyroglobulin Liotrix	Antiangular Agents
25	Thyroid Drugs	Nitroglycerin Isosorbide Dinitrate Isosorbide Mononitrate
	Iodine Propylthiouracil Methimazole	Antiarrhythmic Agents
30	Parathyroid Drugs	Moricizine Quinidine Procainamide Disopyramide
	Calcitonin Etidronate Pamidronate Alendronate	Lidocaine Tocainide Mexiletine Flecainide Encainide
35	Gallium Nitrate	Amiodarone
	Vitamins	Respiratory Drugs
40	Vitamin A Vitamin D Vitamin E Vitamin B1 Vitamin B2 Vitamin B3 Vitamin B6 Vitamin B12	Bronchodilators
45	Vitamin C (con't. next column)	Albuterol Metaproterenol Terbutaline isoproterenol Ephedrine Theophylline Dyphylline

-14-

	Nasal Decongestants	Antirheumatic Agents
	Phenylpropanolamine	Gold Compounds
5	Pseudoephedrine	Penicillamine
	Phenylephrine	Azathioprine
	Ephedrine	Methotrexate
	Naphazoline	
	Oxymetazoline	
10	Tetrahydrozoline	
	Xylometazoline	
	Propylhexedrine	
		Agents for Gout
		Probenecid
		Sulfinpyrazone
		Allopurinol
		Colchicine
	Gastrointestinals	Agents for Migraine
	Sucralafate	Sumatriptan
15	Metoclopramide	Methysergide
	Cisapride	Ergotamine Derivatives
	Laxatives	
	Mesalamine	
	Olsalazine	
	Antidiarrheals	
20	Famotidine	
	Nizatidine	
	Cimetadine	
	Rantidine	
	Omeprazol	
25	Cifaxpride	
	Miscellaneous	
	Finasteride	
	Lamsoprazole	
30	Papaverine	
	Prostaglandins	
	Amphetamines	
	Dextroamphetamine	
35		
	Anorexiants	
	Phentermine	
	Benzphetamine	
	Phendimetrazine	
40	Diethylpropion	
	Mazindol	
	Fenfluramine	
	Dexfenfluramine	
45		
		Antianxiety Agents
		Meprobamate
		Alprazolam
		Chlordiazepoxide
		Clonazepam
		Clorazepate
		Diazepam
		Halazepam
		Lorazepam
		Oxazepam (con't. next page)

-15-

	Prazepam	Antipsychotic Agents
	Buspirone	Chlorpromazine
	Hydroxyzine	Promazine
5	Doxepin	Trifluoperazine
	Chlormezanone	Thioridazine
	Anticonvulsants	Mesoridazine
	Phenytoin	Acetophenazine
10	Mephenytoin	Perphenazine
	Ethotoin	Fluphenazine
	Ethosuximide	Trifluoperazine
	Methsuximide	Chlorprothixene
	Phensuximide	Thiothixene
15	Paramethadione	Haloperidol
	Trimethadione	Molindone
	Clonazepam	Loxapine
	Clorazepate	Clozapine
	Valproic Acid	Risperidone
	Lamotrigine	Pimozide
20	Primidone	Prochlorperazine
	Gabapentin	Other Psychotherapeutic Agents
	Phenacemide	Lithium
	Carbamazepine	Methylphenidate
25	Phenobarbital	Tacrine
	Antidepressants	Pemoline
	Amitriptyline	Antimicrobials
	Clomipramine	Antibacterials
30	Doxepin	Penicillins
	Imipramine	Cephalosporins
	Trimipramine	Carbapenems
	Amoxapine	Monobactams
	Desipramine	Chloramphenicol
35	Nortriptyline	Fluoroquinolones
	Protriptyline	Tetracyclines
	Venlafaxine	Macrolides
	Maprotiline	Spectinomycin
	Trazodone	Vancomycin
40	Bupropion	Lincosamides
	Fluoxetine	Aminoglycosides
	Paroxetine	Colistin
	Sertraline	Polymixin B
	Fluvoxamine	Bacitracin
45	Tranylcypromine	Novobiocin
	Phenelzine	Metronidazole
	Nefazodone	

	Antifungals	Amantadine
	Flucytosine	Foscarnet
	Nystatin	Didanosine
	Miconazole	Acyclovir
5	Ketoconazole	Ganciclovir
	Amphotericin B	Zalcitabine
	Griseofulvin	Rimantadine
	Fluconazole	Miscellaneous Anti-infectives
	Itraconazole	Trimethoprim
10	Sulfonamides	Trimethoprim-
	Sulfadiazine	Sulfamethoxazole
	Sulfacytine	Erythromycin-
	Sulfamethoxazole	Sulfisoxazole
	Sulflamethiazole	Furazolidone
15	Antimalarials	Pentamidine
	Quinine Sulfate	Eflornithine
	Mefloquine	Atovaquone
	Quinacrine	Trimetrexate Glucuronate
	Doxycycline	Leprostatics
20	4-Aminoquinolone	Dapsone
	Compounds	Clofazime
	8-Aminoquinolone	Antihelmintics
	Compounds	Mebendazole
	Folic Acid Antagonists	Diethylcarbamazine
25	Antituberculous Drugs	Citrate
	Isoniazid	Pyrantel
	Rifampin	Thiabendazole
	Rifabutin	Piperazine
	Ethambutol HCl	Quinacrine
30	Pyrazinamide	Niclosamide
	Aminosalicylate Sodium	Oxamniquine
	Ethionamide	Praziquantel
	Cycloserine	Antihistamines
	Streptomycin Sulfate	Diphenhydramine
35	Capreomycin	Chlorpheniramine
	Amebicides	Pyrilamine
	Paromomycin	Doxepin
	Iodoquinol	Carbinoxamine
	Metronidazole	Clemastine
40	Emetine	Tripelennamine
	Chloroquine	Brompheniramine
	Antivirals	Dexchlorpheniramine
	Famciclovir	Triprolidine
	Stavudine	Methdilazine
45	Zidovudine	Promethazine
	Ribavarin (con't. next	Trimeprazine (con't. next page)
	column)	

-17-

	Hydroxyzine HCl	Desoximetasone
	Azatadine	Fluocinolone
	Cyproheptadine	Halcinonide
	Phenindamine	Clocortolone
5	Astemizole	Flurandrenolide
	Loratadine	Fluticasone
	Terfenadine	Mometasone
	Cetirizine	Aclometasone
10	Antimetabolites	Desonide
	5-Fluorouracil	Fludrocortisone
	6-Mercaptourine	Local Anesthetics
	Mycophenolic Acid	Dibucaine
	Methotrexate	Lidocaine
15	Cytarabine	Benzocaine
	Floxuridine	Butamben Picrate
	Thioguanine	Tetracaine
	Anticholinergics	Dyclonine
20	Atropine	Pramoxine
	Scopolamine	Prilocaine
	Homatropine	Antiplatelet Drugs
	Tropicamide	Dipyridamole
	Pirenzepine	Ticlopidine
25	Isopropamide	Warfarin
	Propantheline	Coumarin
	Methscopolamine	Non-steroidal Antiinflammatory Agents
	Methantheline	Fenoprofen
	Trihexyphenidyl	Ibuprofen
30	Benztropine	Flurbiprofen
	Biperiden	Ketoprofen
	Steroidal Antiinflammatory Agents	Naproxen
	Cortisone	Oxaprozin
35	Hydrocortisone	Diclofenac
	Hydrocortisone Acetate	Etodalac
	Prednisone	Indomethacin
	Prednisolone	Ketorolac
	Triamcinolone	Nabumetone
40	Methylprednisolone	Sulindac
	Dexamethasone	Tolmentin
	Betamethasone	Meclofenamate
	Clobetasol	Flufenamic Acid
	Diflorasone	Mefenamic Acid
45	Halobetasol	Meclofenamic Acid
	Amicinonide (con't. next column)	Piroxicam
		Salicylates (con't. next page)

	Diflunisal	Carteolol
	Indomethacin	Nadolol
	Phenylbutazone	Penbutolol
	Oxyphenbutazone	Pindolol
5	Sulfinpyrazone	Sotalol
	Allopurinol	Timolol
	Penicillamine	Labetalol
	Colchicine	
	Probenicid	
10	Sunscreen Agents	Ace Inhibitors
	Oxybenzone	Benazepril
	Dioxybenzone	Captopril
	p-Aminobenzoic Acid	Enalapril
15	Ethyl Dihydroxy Propyl PABA	Fosinopril
	Padimate 0	Lisinopril
	Glyceryl PABA	Moexipril
	Cinoxate	Quinapril
20	Ethylhexyl p-methoxycinnamate	Ramipril
	Octocrylene	Calcium Channel Blockers
	Octyl Methoxycinnamate	Diltiazem
	Ethylhexyl salicylate	Verapamil
	Homosalate	Nifedipine
25	Octyl Salicylate	Felodipine
	Menthyl Anthranilate	Nicardipine
	Digalloyl Trioleate	Nimodipine
	Avobenzone	Nisoldipine
	Muscle Relaxants	Isradipine
30	Carisoprodol	Bepridil
	Chlorphenesin	Amlodipine
	Chlorzoxazone	Nisoldipine
	Cyclobenzaprine	
	Metaxalone	Alpha Blockers
35	Methocarbamol	Methyldopa
	Orphenadrine	Clonidine
	Diazepam	Phentolamine
	Baclofen	Guanabenz
40	Antihypertensives	Phenoxybenzamine
	Beta-Blockers	Guanfacine
	Propranolol	Yohimbine
	Acebutolol	Reserpine
	Betaxolol	Guanethidine
45	Bisoprolol	Guandrel
	Esmolol (con't. next	Doxazosin
	column)	Prazosin
		Terazosin
		Vasodilators
		Hydralazine
		Minoxidil
		Nitroglycerin (con't. next
		page)

-19-

	Isosorbide Dinitrate Isosorbide Mononitrate Papaverine	Oxymorphone Oxycodone Meperidine Methadone Propoxyphene Tramadol Acetaminophen Pentazocine Fentanyl Salicylates
5	Diuretics Thiazides Loop Diuretics Spironolactone Triamterene Acetazolamide Methazolamide Dichlorphenamide	Sex Hormones Estogens Estriol Estradiol Estrone
10		Testosterone Methyltestosterone Progesterone Medroxyprogesterone Hydroxyprogesterone Norethindrone Megesterol
15	Antiemetics Chlorpromazine Trifluromazine Perphenazine Prochlorperazine Promethazine Thiethylperazine Metoclopramide Cyclizine Meclizine Buclizine Dimenhydrinate Trimethobenzamide Scopolamine Diphenidol Benzquinamide Hydroxyzine	Pituitary Hormones DDAVP Methylergonovine
20		Uterine Hormones Carboprost Dinoprostone
25		Adrenal Steroid Inhibitors Aminoglutethimide
30		
35	Analgesics Codeine Hydrocodone Hydromorphone Morphine (cont. next column)	

In one preferred embodiment, the drug is ketoprofen.

Finally, the carrier and drug release agent form a polymeric composition which provides the separate penetration enhancement of facilitating the rapid release of the medication from the cream upon topical application to the patient. The purpose of this combination of materials is to provide for penetration enhancement of a different type than that of the organogel, i.e., by effecting

-20-

rapid release of the drug from the cream and transport by the carrier out of the cream and into the skin through the enhanced openings in the stratum corneum.

The drug release agent may be any of a variety of polyoxymers, i.e., polyoxyalkylene derivatives of propylene glycol. Preferred are those which 5 contain mixtures of polyoxyethylene and polyoxypropylene polymeric derivatives of propylene glycol or methyl oxirane polymers. By acting essentially as an emulsifier, stabilizer and dispersing agent, the polyoxymer facilitates the separation of the drug or medication from the other components of the cream and transfers it to the carrier, which will normally be water or a low molecular 10 weight alcohol or organic solvent. Useful polyoxymers are available under the trademark "Pluronic" from Wyandotte Chemical Company.

The concentration of the carrier provided with the drug release agent as a mixture in the cream will determine the particular diffusion coefficient of the drug. With higher concentrations of the carrier, the diffusion coefficient will be 15 lower and the drug will be absorbed more slowly and produce more local effects. Conversely, lowering the concentration of the carrier will speed the absorption of the drug and enhance the ability of the drug to be absorbed systemically. The normal concentration of the drug release agent in the mixture with the cream will be approximately 20% to 30%, with the balance being the carrier, during the 20 formation of the carrier/drug release agent mixture.

The overall concentrations of the various components in the composition will generally be in the ranges of:

Medication	<1%-20%
Solvent for medication	<1%-20%
25 Organogel	20%-40%
Carrier/release agent	40%-70%

-21-

It will of course be understood that these ranges represent the typical ranges for the specific example upon which the Figure is based, i.e., an example with a lecithin organogel, ketoprofen as the drug, and a "Pluronic NF-127" polyoxymer as the drug release agent. In general the ranges for other 5 compositions of this invention in which other suitable organogels, drugs, carriers and release agents are used will be similar, and those skilled in the art will have no difficulty formulating suitable compositions from the description herein.

Other factors will need to be considered in preparing specific formulations. If the carrier concentration in the cream lies above the useful range, it becomes 10 relatively stiff and difficult to apply, or, conversely, if the concentration falls below the suitable level, the cream will have a tendency to separate. Further, the pH of the cream must be adjusted to match the pH of the solubilized medication component to maximize the amount of non-ionized drug present in the cream. All suitable medications have acid/base characteristics that can be altered by 15 adjustment of the pH of the composition. The greater proportion of non-ionized drug present, the greater the drug's solubility and the greater the ability for larger quantities of the drug to be transported transdermally. The control of the pH can also be used to determine whether the drug is likely to become absorbed 20 systemically or to be absorbed locally, since the speed of transdermal transport will be dependent on the pH.

The physical properties of the cream will also be important. As noted the viscosity must be such that it can be applied topically and conform to and adhere to the patient's skin for a period of time sufficient for a significant portion of the medication to be delivered transdermally to the patient. It must also be capable 25 of being removed from the patient's skin with ordinary physiologically acceptable cleansers or solvents, so that the cream may be removed if medically necessary,

-22-

or the residue may be removed once the treatment time period for each administration has been completed. The components must be capable of being blended into a smooth, homogenous mixture with a cream- or lotion-like consistency and appearance, which either has a natural light colored 5 appearance or can be lightly tinted if flesh-compatible tones are desired. The cream must also be capable of being covered with a light gauze or other type of dressing if desired, particularly where the cream would otherwise be in contact with the patient's clothing.

Adjustment of pH, effects of concentration and achievement of suitable 10 physical properties in compositions containing polyoxymers have been studied and reported by Chi et al., *J. Pharm. Sci.*, **80** (3): 280-283 (1991). Reference is made to that article, and the prior references reported therein, for guidance in determining practical limits of pH, concentration, viscosity and the like when varying the specific materials herein. The techniques and methods reported 15 there are quite suitable for use in the present invention.

Examples of the formation of different components are given below:

EXAMPLE 1

Formation of a Lecithin Organogel

A number of different lecithin organogels were formed by mixing different 20 quantities of granular lecithin soya with isopropyl palmitate and a solvent. In three different typical compositions the respective amounts of lecithin soya and isopropyl palmitate were 25%/75%, 50%/50%, and 75%/25%. The first composition can be characterized as a thin oil, the second as a medium oil and the third as a heavy oil. In all cases the lecithin granules and isopropyl palmitate 25 were allowed to sit for several hours, commonly overnight, by the end of which a liquid of oil or syrup consistency had formed. Alternatively one can mix the

-23-

lecithin soya and the isopropyl palmitate at 50° to 60°C until the dissolution is complete.

At any point during formation of the mixture one can also add the drug or medication. If the latter is soluble in alcohol it may be previously dissolved in the
5 alcohol and the alcohol/drug mixture incorporated into the lecithin soya and isopropyl palmitate mixture.

EXAMPLE 2

Formation of a Carrier/Drug Release Agent Component

A polymeric gel for use as a carrier was formed by mixing 20 grams of a
10 commercial polyoxymer designated as "Pluronic NF-127" with 0.2 g of pure potassium sorbate and adding sufficient refrigerated purified water to bring to volume of 100 ml. Other similar compositions were formed with 30 g and 40 g of the "Pluronic NF-127" respectively. A typical commercial mixer was used to mix the material. Once all of the granules of the polymeric material had been
15 wetted the gel was refrigerated so that dissolution took place upon cooling in the refrigerator. The compositions must be maintained under refrigeration because at ambient conditions they will solidify, since (as opposed to water) polyoxymer mixtures as prepared herein solidify when heated and liquefy when cooled. Stock solutions of these materials may be made and kept in refrigerated storage
20 for repeated use in the formulation of the compositions of the present invention.

EXAMPLE 3

Mixture of a Cream Containing Medication, Lecithin Organogel and Carrier/Drug Release Agent

In a typical procedure equivalent weights of the lecithin soya and the
25 isopropyl palmitate are combined and a small quantity of sorbic acid is incorporated to control pH. The mixture is stirred until a syrup or oil consistency is obtained. Large quantities may be prepared and kept as a stock solution. The

-24-

drug or medication, e.g., ketoprofen, is dissolved in water, alcohol or an equivalent solvent by using a the minimal amount of solvent necessary to obtain complete solubilizing. The dissolved drug is added to a small portion of the lecithin organogel and stirred to disperse the drug in the gel. The mixture of the 5 carrier and the polyoxymer is then added to bring the entire formulation to the desired volume, and, if necessary, the pH of the cream is adjusted.

It will be evident that there are numerous embodiments of this invention which, while not expressly described above, are clearly within the scope and spirit of the invention. The above description is therefore intended to be 10 exemplary only, and the scope of the invention is to be limited solely by the appended claims.

WE CLAIM:

-25-

CLAIMS

1. A composition useful for diffusional transdermal delivery of medication to a patient, characterized by inclusion of
 - a. a medication capable of being administered transdermally;
 - 5 b. a solvent for said medication;
 - c. a first penetration enhancer which improves diffusion of said medication into and within said patient's skin; and
 - d. a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration;
- 10 said composition having a viscosity in a range such that when applied topically, said composition conforms to and adheres to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally to said patient.
- 15 2. A composition as in Claim 1 wherein said medication is a lipophilic, hydrophilic or amphoteric therapeutic compound.
3. A composition as in Claim 1 or 2 wherein said first penetration enhancer is an organogel and has the property, when applied topically to a patient's skin, 20 of enlarging openings in the stratum corneum, whereby said medication can diffuse through said enhanced openings at a rate greater than its diffusion rate through corresponding unenlarged openings.
4. A composition as in Claim 3 wherein said organogel is a fatty acid phospholipid emulsifying agent and a fatty acid or ester thereof.

-26-

5. A composition as in Claim 1 wherein said second penetration enhancer alters the interaction between said medication and said composition to improve diffusion of said medication out of said composition for transdermal migration.
- 5 6. A composition as in Claim 5 wherein said second penetration enhancer is a polyoxymer.
7. A composition as in Claim 1 further characterized by including:
 - a. <1 to 20 parts by weight of said medication capable of being administered transdermally;
 - b. <1 to 20 parts by weight of said solvent for said medication;
 - c. 20 to 40 parts by weight of said first penetration enhancer which improves diffusion of said medication into and within said patient's skin; and
 - d. 40 to 70 parts by weight of said a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration.
8. A method for the preparation of a therapeutic composition to be transdermally administered, characterized by inclusion of the following steps:
 - 20 a. solubilizing a medication capable of being administered transdermally;
 - b. forming an organogel comprising a first penetration enhancer which improves diffusion of said medication into and within said patient's skin, and a solvent for said solubilized medication;
 - c. forming a polymeric component comprising a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration; and

-27-

d. blending said solubilized medication, organogel and polymeric component to form said composition having a viscosity in a range such that when applied topically, it will conform to and adhere to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally

5 to said patient.

9. A method as in Claim 8 wherein said medication is a lipophilic, hydrophilic or amphoteric therapeutic compound.

10 10. A method as in Claim 8 further characterized by:

a. solubilizing <1 to 20 parts by weight of said medication capable of being administered transdermally;

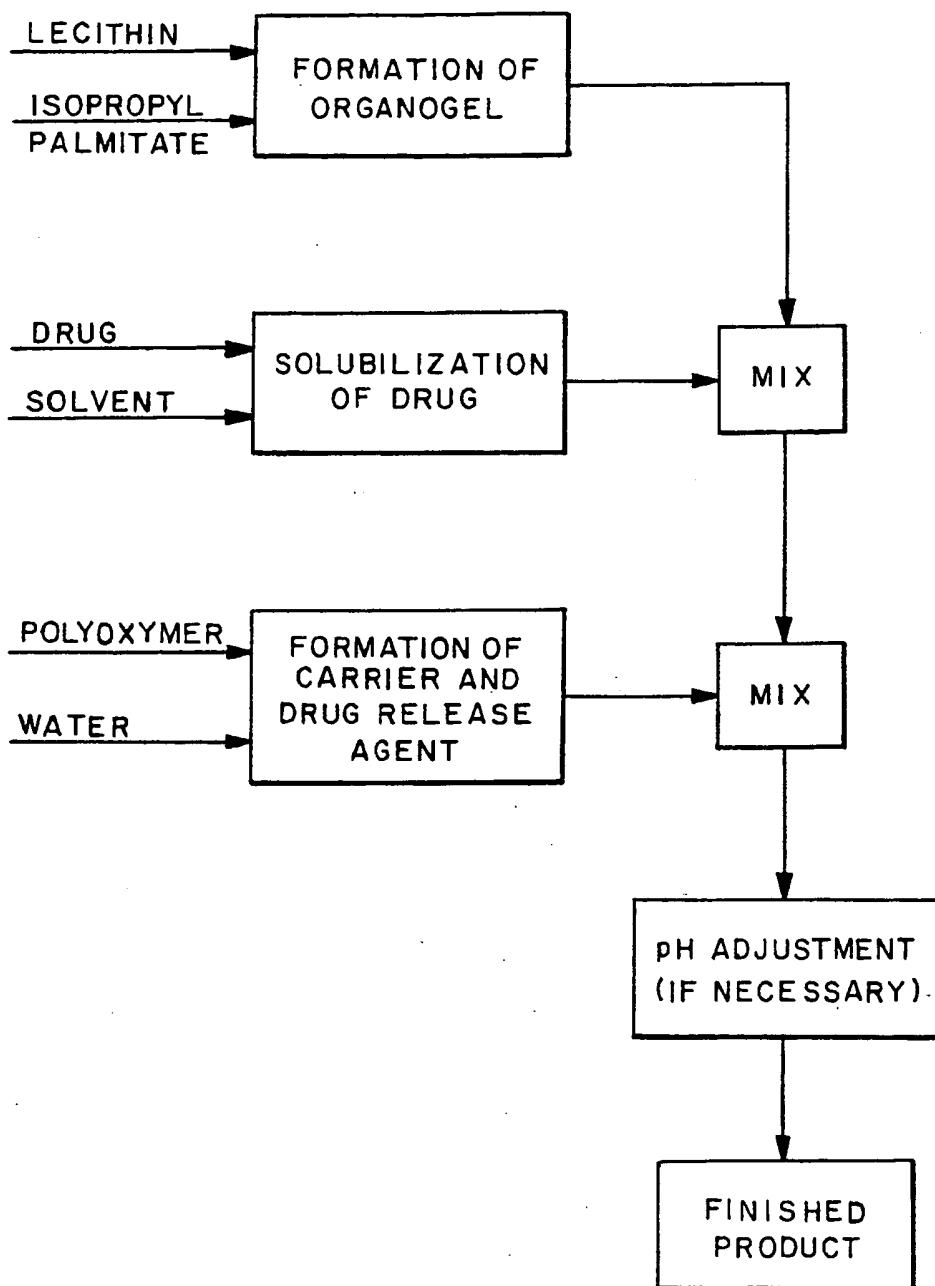
b. forming 20 to 40 parts by weight of said organogel comprising a first penetration enhancer which improves diffusion of said medication into and within

15 said patient's skin, and a solvent for said solubilized medication;

c. forming 40 to 70 parts by weight of said polymeric component comprising a second penetration enhancer which improves diffusion of said medication out of said composition for transdermal migration; and

d. blending said solubilized medication, organogel and polymeric component

20 to form said composition having a viscosity in a range such that when applied topically, it conforms to and adheres to said patient's skin for a period of time sufficient for a significant portion of said medication to be delivered transdermally to said patient.



INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/23014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/10 A61K47/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06636 A (CRANDALL, WILSON) 7 March 1996 see claims 1,3 see page 6, line 23 - page 7, line 1 see page 8, line 6 - line 13 see example 1 ---	1-10
X	US 5 817 699 A (JOHN A. FLORES) 6 October 1998 see claim 1 see column 2, line 9 - line 26 ---	1-10
X	WO 95 11015 A (ELSON, MELVIN) 27 April 1995 see claims 8-12 ---	1-6,8,9 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 1999

Date of mailing of the international search report

02/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 39746 A (ADVANCED POLYMER SYSTEMS) 30 October 1997 see claims 20-23 -----	1-6,8,9
E	WO 99 11208 A (WILLIAMS, C.) 11 March 1999 see claims 1-36 see examples 1-44 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Jonal Application No
PCT/US 98/23014

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9606636	A 07-03-1996	US 5560910 A			01-10-1996
		AU 3417595 A			22-03-1996
		CA 2198362 A			07-03-1996
		EP 0777496 A			11-06-1997
US 5817699	A 06-10-1998	NONE			
WO 9511015	A 27-04-1995	US 5510391 A			23-04-1996
		AU 684850 B			08-01-1998
		AU 8089494 A			08-05-1995
		CA 2174666 A			27-04-1995
		EP 0727985 A			28-08-1996
		JP 9502450 T			11-03-1997
WO 9739746	A 30-10-1997	AU 2804297 A			12-11-1997
WO 9911208	A 11-03-1999	NONE			

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)